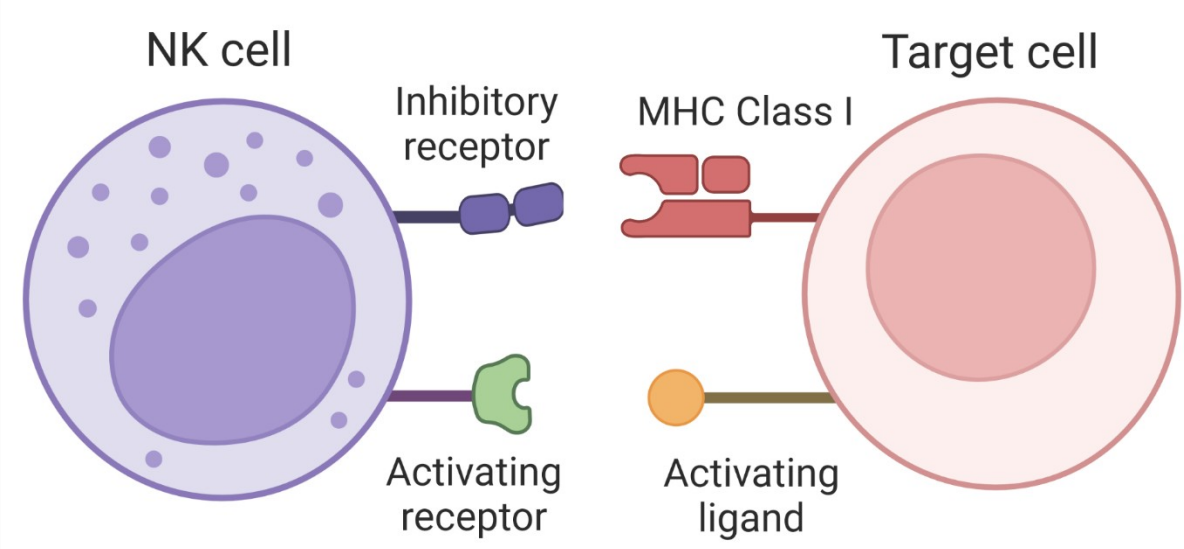
NK cell activation and inhibition

NK Cell Receptors

While on patrol NK cells constantly contact other cells. Whether or not the NK cell kills these cells depends on a balance of signals from activating receptors and inhibitory receptors on the NK cell surface. Activating receptors recognise molecules that are expressed on the surface of cancer cells and infected cells, and ‘switch on’ the NK cell. Inhibitory receptors act as a check on NK cell killing.

Most normal healthy cells express MHC I receptors which mark these cells as ‘self’. Inhibitory receptors on the surface of the NK cell recognise cognate MHC I, and this ‘switches off’ the NK cell, preventing it from killing. Cancer cells and infected cells often lose their MHC I, leaving them vulnerable to NK cell killing.

Once the decision is made to kill, the NK cell releases cytotoxic granules containing perforin and granzymes, which leads to lysis of the target cell.



The target cell on its cell surface expresses an MHC class 1 molecule and an activating ligand. The proximal NK cell expresses on the cell surface an ihibitory receptor, which seeks the MHC 1 to recognise the cell as 'self' and 'switch off' the NK cell. The NK cell has an activating receptor on its surface too, which seeks activating ligands on the target cell, to 'switch on' the NK cell.

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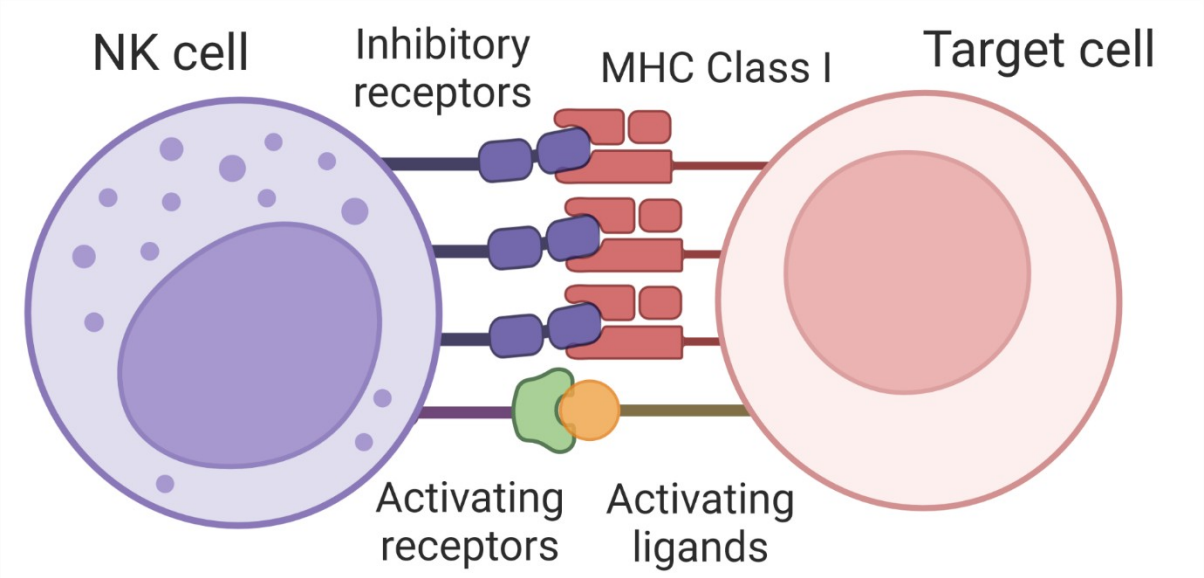
NK Inhibition

The genes for both MHC I and the NK cell inhibitory receptors which recognise them vary a lot between individuals. The versions (or alleles) of

these genes a person carries have been linked to their ability to fight HIV infection and their risk of some autoimmune diseases.

NK cell varieties also change with age and are affected by chronic viral infections such as cytomegalovirus (CMV).



The target cell on its cell surface expresses a higher number of MHC class 1 molecule compared to the number of its activating ligands being expressed on the cell surface. The MHC 1 molecules attach to their corresponding inhibitory receptors on the NK cell surface whilst the activating ligands attach to the activating receptors on the NK cell. This multiple binding of MHC 1 with inhibitory receptors on NK cell stops it from attacking the target cells.

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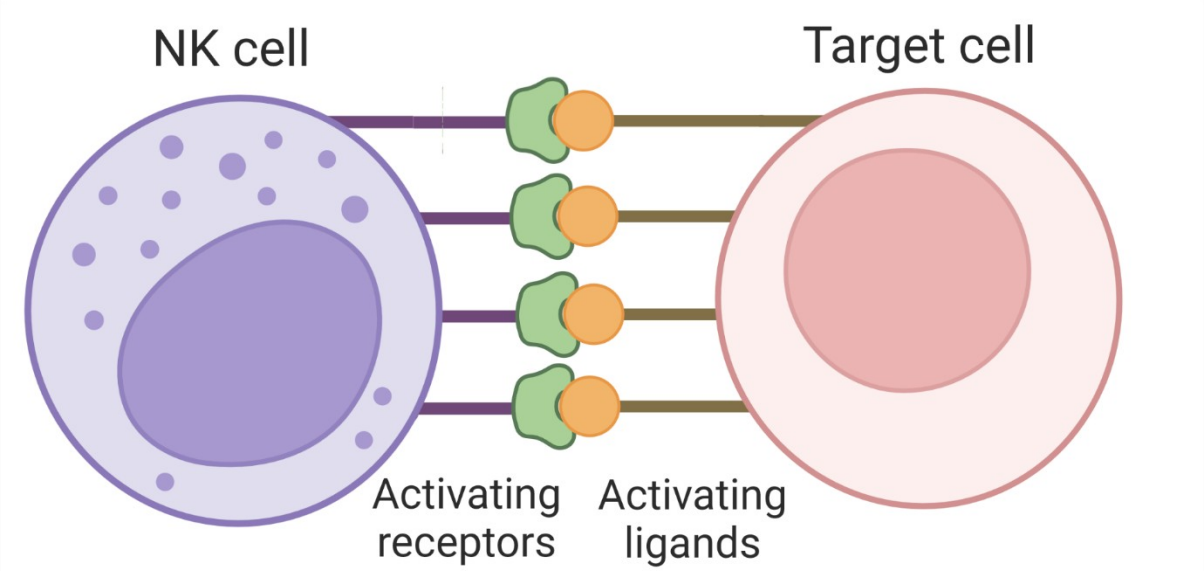
NK Activation

Because of their ability to kill tumour cells, NK cells are an attractive target for cancer immunotherapies. Some therapeutic monoclonal antibodies rely on NK cell killing. Researchers are also developing treatments to activate NK cells using small molecules or cytokines, and even testing genetically modified living NK cells as therapies.



"In reduced NK cell inhibition, a target cell which can be a tumour cell or virally-infected cell has no MHC class 1 molecules and normal level of activating ligands on their surface. There is binding of large number of activating ligands to their corresponding activating receptors on NK cell surface. There is no delivery of a strong inhibitory signal due to the lack of MHC 1. NK cell will attack and eliminate the target cell. "

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